

### REMARKS

Claims 1-26 and 41-44 constitute the pending claims in the present application prior to Amendment. Claims 1-26 are currently under consideration having been elected with traverse. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claims 1-4, 7-8, 15 and 17- 21 have been amended. Claims 5-6, 9-14, 16 and 22-25 have been canceled, without prejudice. Applicants reserve the right to prosecute claims of similar or differing scope.

Claim 1 has been amended to recite "an undifferentiated cell having activin receptors responsive to activin." Support for the amendment can be found, for example, at page 4, lines 26-30; page 4, line 34 to page 7, line 2; page 8, lines 13-15; page 12, lines 9-11; and in the Examples (all page references are provided using the substitute specification.).

Claim 1 has also been amended to recite that the undifferentiated cell is provided in a culture of two or more cells in vitro. Support for the amendment can be found, for example, at page 2, lines 10-17; page 2, line 30 to page 3, line 2; page 3, lines 8-17; page 5, lines 16-24; page 5, line 35 to page 6, line 2; page 21, lines 7-9; and page 24, lines 8-13.

Claim 1 has further been amended to specify the first agent. Support for the amendment can be found in claims 4 and 7 as originally filed.

Claim 1 has been amended to recite providing the cells with a second agent. Support for the amendment can be found in claim 15 as originally filed.

Claims 2-4, 7-8, 15 and 17-21 have been amended to use language consistent with that of claim 1 and to correct obvious typographical errors.

No new matter has been added.

1. The specification is objected to as containing certain typographical errors. Applicants are unable to find the cited typographical errors in the specification outside of the claims. Applicants request that the Examiner specifically point out any typographical errors in the specification or that the Examiner correct such errors by Examiner's amendment.
2. Claims 24 and 25 are objected to for containing a typographical error. Claims 24 and 25 have been canceled, thereby obviating the objection.

3. Applicants note with appreciation that the substitute specification submitted November 25, 2003 has been entered. Applicants note that the requirement for a new oath has been withdrawn.

4. Claims 1-18, 21, and 25-26 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-8 of U.S. Patent No. 6,686,198. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

5. Claims 1-21 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims. For clarity, Applicants will address the aspects of the rejection in the order in which they appear in the Office Action.

First, the Examiner states that the body of claim 1 has no step or requirement for development of a neuronal cell phenotype. Claim 1 has been amended to recite that the first agent and second agent are provided in amounts sufficient to induce differentiation of said cell to a neuronal cell phenotype, such that the claimed method results in the effect recited in the preamble. Applicants note that claim 25 has been canceled.

Second, the Examiner states that the claimed method are only enabled for specific situations involving *Xenopus* two cell embryos, follistatin, inhibin, the truncated activin receptor and the injection of RNA. Applicants respectfully disagree, and maintain that the instant claims are fully enabled by the specification, including the Examples. The Examiner provides no evidence or reasoning as to why the claimed methods are allegedly enabled for only the specific situations. In particular, the Examiner has not followed the *Wands* factors for assessing enablement.

Third, the Examiner states that the claimed methods require that one know the identity of growth factors from the TGF- $\beta$  family that normally induce a cell to differentiate to a non-neuronal phenotype and that one know the identity of agents that antagonize the biological action of these growth factors. In order to expedite prosecution, the claims have been amended to

remove recitation of such growth factors, thereby rendering this aspect of the rejection moot. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Fourth, the Examiner states that many of the claimed methods require that one know that an appropriate receptor for a growth factor is present on the cell surface. In order to expedite prosecution, claim 1, from which all other claims under consideration depend, has been amended to recite that a cell has activin receptors responsive to activin. The Examiner has acknowledged enablement with respect to the truncated activin receptor and has presented no evidence or reasoning with respect to a full length activin receptor. Thus, Applicants believe that the claims as amended are fully enabled by the specification. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Fifth, the Examiner states that the examples of the specification provide no basis upon which to predicate success of the method on other cell types or organisms. In order to expedite prosecution, claim 1, from which all other claims under consideration depend, has been amended to recite undifferentiated cells. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. The examples of the specification are predictive of undifferentiated cells. With respect to organisms, Applicants disagree with the Examiner's characterization of Applicants' result, as well as with the characterization of the unpredictability in the art. Numerous publications, based on work done in a wide range of systems, support enablement of the full scope of the claimed subject matter. Most notable is the large number of articles demonstrating a role for activin antagonism in mammalian neural development and regeneration. For example, Tuuri et al. reveal an overlapping expression pattern for activin and follistatin in the adult human brain (Tuuri et al., 1994, enclosed herewith as Exhibit 1). Mendis et al. reveal expression of a follistatin related protein, SC1, in the rat brain (Mendis et al., 1996, enclosed herewith as Exhibit 2). Additionally, Mendis et al. demonstrate upregulation of SC1 expression in the brain following injury. This is especially important given the current understanding for the role of a population of stem cells resident in adult tissue in regeneration following injury. Finally, Fainsod et al. demonstrates that follistatin induces neural fate in both *Xenopus* embryos and in cultured P19 cells (Fainsod et al., 1997, enclosed herewith as Exhibit 3). Applicants cite these examples to illustrate that the

prevailing view in the art is that antagonism of activin activity induces neural differentiation or survival, and that, contrary to the contentions of the Office Action, this view is not held uniquely within the community of amphibian researchers. Thus, the instant claims are enabled for a multitude of organisms.

Sixth, the Examiner states that agents may not be accessible to the intended cell. In order to expedite prosecution, claim 1, from which all other claims under consideration depend, has been amended to recite "providing" in lieu of "contacting." "Providing" is understood to encompass the delivery of an activin antagonist by any means well known in the art including contacting cells with a protein, injecting an mRNA encoding a protein, infecting cells with a retrovirus comprising an mRNA encoding a protein, etc. Such methods of expressing proteins in cells are not only well within the tool-box of methods commonly employed by one of skill in the art, but are also outlined in the specification and were clearly contemplated by Applicants at the time of filing.

Seventh, the Examiner alleges that the examples do not support methods using dissociated cell cultures or in isolated single cells. Applicants contend that the claims are directed to cells in culture, and that cells in culture will have interactions with each other (e.g., cells in culture provide a microenvironment where inductive and other interaction can occur). To expedite prosecution of the present application, Applicants have amended the claims to more explicitly point out that the cells in culture are not single cells. Accordingly, the cells in culture can participate in cell to cell communication and inductive interactions which take place in any in vivo or in vitro environment where cells can contact each other. Applicants' amendment is not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Eighth, the Examiner refers to publications which allegedly dispute the enablement of the presently claimed invention. The ability to identify individual publications or specific dominant negative constructs that do not meet the limitations of the pending claims does not undermine the enablement of the presently claimed invention. The MPEP provides two passages that are especially instructive in evaluating claims when some contradictory evidence is uncovered. MPEP 2164.08(b) states that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be

inoperative or operative with expenditure of no more effort than is normally required in the art.” MPEP 2164.05 instructs that enablement must be based on an analysis of the evidence as a whole. These sections of the MPEP recognize that there can be examples which fall within the metes and bounds of a claim which do not work as recited in the claim, but that such examples do not undermine the enablement of the invention as a whole. Maintenance of the rejection under 35 U.S.C. 112, first paragraph, would deprive an Applicant of a patent based on the identification of isolated circumstances under which the claimed subject matter is inoperative and is clearly improper.

Ninth, the comments with respect to claims 6 and 10-11 are moot in view of the cancellation of these claims.

Tenth, the Examiner states that the metes and bounds of various growth factors cannot be determined. The Examiner simply asserts this without providing any further reasoning or evidence. Applicants maintain that one of ordinary skill in the art would readily be able to identify the metes and bound of these terms.

Eleventh, the Examiner states that the specification does not enable how to identify specific neural progenitor cells. One of ordinary skill in the art would readily be able to identify progenitor cells within the scope of the claims, based both on the knowledge in the art and the passage at page 11, line 30 through page 12, line 13 of the substitute specification.

Twelfth, the Examiner states that the metes and bounds of a "peptidergic cell" are not known. The meaning attributed to this term by the Examiner is incorrect. According to Stedman's Medical Dictionary, 27th Edition, "peptidergic" refers to "nerve cells or fibers that are believed to employ small peptide molecules as their neurotransmitters" (see Exhibit 4). Thus, one of ordinary skill in the art would readily be able to determine the metes and bounds of the recitation.

In summary, the instant claims are fully enabled by the specification and do not represent "an invitation to experiment." Reconsideration and withdrawal of the rejection are respectfully requested.

6. Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. In order to expedite prosecution, claims 22-24 have

been canceled. Applicants reserve the right to prosecute claims of similar or differing scope in a continuation application. Withdrawal of the rejection is respectfully requested.

7. Claims 6, 9-10, 15 and 24 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. Claims 6, 9-10 and 24 have been canceled, thereby rendering the rejection moot with respect to these claims. The Examiner objects to the recitation of "such as" in claim 15. The recitation of "such as" has been eliminated from claim 15. Withdrawal of the rejection is respectfully requested.

8. Claims 1-4, 17, 21-23 and 25-26 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Fukui *et al.* The Examiner states that Fukui *et al.* disclose adding *Xenopus* follistatin protein to ectoderm sheets of the late blastula of *Xenopus* to suppress or inhibit mesoderm induction in the presence of *Xenopus* activin-AB. Claim 1, from which all other claims under consideration depend, has been amended to recite that the method also comprises providing a cell with a second agent which agent is a neurotrophic factor that enhances a particular differentiation fate of the cell, where the first agent and the second agent are provided in amounts sufficient to induce differentiation of a cell to a neuronal cell phenotype. Fukui *et al.* does not disclose providing a first agent and a second agent in amounts sufficient to induce differentiation of a cell to a neuronal cell phenotype. Thus, Fukui *et al.* does not disclose all limitations of the instant claims, such that the cited reference does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

9. Claims 1-4, 22-23 and 25-26 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Yamada *et al.* The Examiner states that Yamada *et al.* discloses adding activin and follistatin proteins to a human myelocytic cell line, which resulted in differentiation to non-neuronal phenotypes (with activin) or inhibition of differentiation (with follistatin). Claim 1, from which all other claims under consideration depend, has been amended to recite that a first agent and a second agent are provided in amounts sufficient to induce differentiation of a cell to a neuronal cell phenotype. Yamada *et al.* does not disclose inducing a cell to differentiate to a neuronal cell phenotype. Thus, Yamada *et al.* does not disclose all limitations of the instant

claims, such that the cited reference does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

10. Claims 1-4, 22 and 25-26 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Hashimoto *et al.* The Examiner states that Hashimoto *et al.* discloses adding follistatin to various neural cells to stimulate neural differentiation and adding activin to inhibit neural differentiation. Claim 1, from which all other claims under consideration depend, has been amended to recite that a first agent and a second agent are provided in amounts sufficient to induce differentiation of a cell to a neuronal cell phenotype. Yamada *et al.* does not disclose adding a first agent and a second agent to induce a cell to differentiate to a neuronal cell phenotype. Thus, Hashimoto *et al.* does not disclose all limitations of the instant claims, such that the cited reference does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

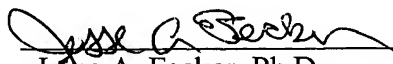
While Applicants acknowledge that a reiteration step, which mirrors the preamble, has been added to the claims, Applicants respectfully disagree that the claims are otherwise incomplete and not enabled by the specification.

**CONCLUSION**

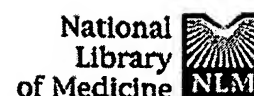
In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. HUIP-P04-009.**

Respectfully Submitted,

Date: November 10, 2006

  
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## EXHIBIT 1



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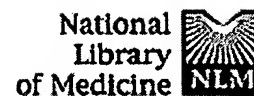
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(6):1521-4Related Articles, **NEW Books**,  
LinkOut**The tissue distribution of activin beta A- and beta B-subunit and follistatin messenger ribonucleic acids suggests multiple sites of action for the activin-follistatin system during human development.****Tuuri T, Eramaa M, Hilden K, Ritvos O.**

Department of Bacteriology and Immunology, University of Helsinki, Finland.

Activins have potent effects on early morphogenetic events during amphibian embryogenesis but no evidence for their role during human development other than their expression in steroidogenic tissues has been reported. We previously showed the expression of the activin type II and IIB receptor mRNAs in several tissues of the mid-gestational human fetus with highest expression levels in developing neural, muscular and exocrine glandular organs. We now report that the mRNA transcripts for activin beta A- and beta B-subunits and for the activin-binding protein follistatin are found co-expressed in several of these extragonadal tissues. Their mRNAs were detected by Northern analyses using specific single-stranded 32P-labeled cDNA probes. In the nervous system, both activin beta A- and beta B-subunit transcripts were expressed in the cerebrum and spinal cord. Follistatin was abundantly expressed in the spinal cord whereas weaker signals were observed in the cerebrum and cerebellum. In the muscular system, beta A-subunit was abundantly expressed in the heart but to a lesser extent in the skeletal muscle while the opposite was observed for follistatin. Follistatin, and activin beta A- and beta B-subunit mRNAs were also detected in developing kidney, salivary gland, liver, and adrenal. The predominance of beta A-subunit mRNAs in the bone marrow and beta B-subunit mRNAs in the salivary gland suggests specific roles for activin A and B, respectively, in these tissues. No hybridization signal was detected for the inhibin alpha-subunit in non-steroidogenic tissues indicating that, in contrast to activins and follistatin, the effects of inhibins may be restricted to the gonads and adrenals which are known to express high levels of the alpha-subunit transcript. Taken together, our results suggest that the activin-follistatin system regulates the development of several organ systems in the mid-gestational human fetus.



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☐ 1: Brain Res 1996 Aug 19;730(1-2):95-106 Related Articles, **NEW Books**, LinkOut**SC1, a brain extracellular matrix glycoprotein related to SPARC and follistatin, is expressed by rat cerebellar astrocytes following injury and during development.****Mendis DB, Ivy GO, Brown IR.**

Department of Zoology, University of Toronto, Ontario, Canada.

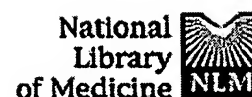
In the nervous system, extracellular matrix components are believed to influence cell shape, proliferation and migration during development and following injury. SC1 is a secreted glycoprotein expressed during neural development and in the adult brain. The molecule shows partial sequence homology to the anti-adhesive extracellular matrix molecule SPARC/osteonectin and to follistatin. We have made a surgical lesion in the adult rat cerebellum and examined changes in SC1 expression at 1 to 14 days after injury. Dual in situ hybridization/immunohistochemistry demonstrated that SC1 mRNA was induced in astrocytes surrounding the wound, reaching maximal levels at 10 days post-lesion. Immunohistochemistry revealed changes in the deposition of SC1 protein in radial fibres of Bergmann glia. SC1 protein was also detected at the border of the lesion, suggesting an association with the glial scar. Double immunohistochemistry with the astrocytic marker GFAP demonstrated that astrocytes also express SC1 during postnatal development.

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## EXHIBIT 3



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FULL-TEXT ARTICLE**The dorsalizing and neural inducing gene follistatin is an antagonist of BMP-4.****Fainsod A, Deissler K, Yelin R, Marom K, Epstein M, Pillemer G, Steinbeisser H, Blum M.**

Department of Cellular Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem, Israel. fainsod@gene.tnd.huji.ac.il

Specific signaling molecules play a pivotal role in the induction and specification of tissues during early vertebrate embryogenesis. BMP-4 specifies ventral mesoderm differentiation and inhibits neural induction in *Xenopus*, whereas three molecules secreted from the organizer, noggin, follistatin and chordin dorsalize mesoderm and promote neural induction. Here we report that follistatin antagonizes the activities of BMP-4 in frog embryos and mouse teratocarcinoma cells. In *Xenopus* embryos follistatin blocks the ventralizing effect of BMP-4. In mouse P19 cells follistatin promotes neural differentiation. BMP-4 antagonizes the action of follistatin and prevents neural differentiation. In addition we show that the follistatin and BMP-4 proteins can interact directly in vitro. These data provide evidence that follistatin might play a role in modulating BMP-4 activity in vivo.

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**peptatin** (pep-sta'tin). An inhibitor peptide from actinomycetes that inhibits pepsin and cathepsin D.

**peptidic** (pep'tik). Relating to the stomach, to gastric digestion, or to pepsin. *[G. peptikos, fr. peptō, to digest]*

**peptidase** (pep'ti-dās). Any enzyme capable of hydrolyzing a peptide bond of a peptide; e.g., carboxypeptidases, aminopeptidases, *syn* peptide hydrolase.

**peptidyl dipeptidase**. *syn* proline dipeptidase.

**peptidyl dipeptidase A**. *syn* peptidyl dipeptidase A.

**peptide** (pep'tid). A compound of two or more amino acids in which a carboxyl group of one is united with an amino group of another, with the elimination of a molecule of water, thus forming a peptide bond,  $-CO-NH-$ ; i.e., a substituted amide. Cf. eupeptide bond, isopeptide bond.

**paracorticotrophic p.**, a p. with ACTH activity, isolated from pituitary extracts.

**neutrophil-activating p. (ANAP)**, *syn* interleukin-8.

**atrial natriuretic p. (ANP)**, the protein fragments that bind to MHC molecules.

**atrial natriuretic p. (ANP)** (na'trē-oo-ret'ik), a 28-amino acid p. (ANP), derived from cardiac atria, several smaller fragments of ANP, and a dimer of  $\alpha$ -ANP with 56 amino acids ( $\beta$ -ANP) that are present in plasma in heart failure. ANP actions include increasing capillary filtration, and renal salt and water excretion, and decreasing arterial pressure and the secretion of renin, angiotensin, aldosterone, and antidiuretic hormone. *syn* atriopeptin, atrionatriin.

**bitter p.'s**, p.'s that have a bitter taste and may spoil certain foods; often contain high proportions of leucyl, valyl, and aromatic amino acyl residues.

**bradykinin-potentiating p.**, *syn* teprotide.

**calcitonin gene-related p. (CGRP)**, a second product transcribed from the calcitonin gene. CGRP is found in a number of tissues including nervous tissue. It is a vasodilator that may participate in the cutaneous triple response.

**cyclic p.**, a p. that forms a ring structure; e.g., tyrocidin A, an antibiotic, is a cyclic decapeptide; valinomycin is a cyclic dodecapeptide.

**gastric inhibitory p. (GIP)**, *syn* gastric inhibitory polypeptide.

**glucagonlike p.**, a gut hormone that slows gastric emptying and stimulates insulin secretion. It may become useful in the future in the treatment of noninsulin-dependent diabetes mellitus, perhaps administered by patch, inhaler, or buccal pellet formulation.

**glucagonlike insulinotropic p.**, an insulinotropic substance originating in the gastrointestinal tract and released into the circulation following ingestion of a meal containing glucose.

**heterodetic p.**, a p. that contains p. bonds as well as covalent linkages between certain amino acyl residues that are not p. bonds; e.g., valinomycin, oxytocin. [hetero- + *G. detos*, bound, fr. *deō*, to bind, + -ic]

**heteromeric p.**, a p. that, on hydrolysis, yields substances other than amino acids in addition to amino acids; e.g., pteroylglutamic acid.

**homodetic p.**, a p. in which all of the covalent linkages between constituent amino acids are p. bonds; e.g., bradykinin. [homo- + *G. detos*, bound, fr. *deō*, to bind, + -ic]

**homomeric p.**, (1) a p. that, on hydrolysis, yields only amino acids; e.g., glutathione; (2) a p. that consists of only one particular amino acid; e.g., alanylalanylalanine.

**peptidase** [EC subclass 3.4], *syn* peptidase.

**parathyroid hormone-related p.**, a hormone that can be produced by tumors, especially of the squamous cell type; massive overproduction can lead to hypercalcemia and other manifestations of hyperparathyroidism. PTHrP exerts a biologic action similar to that of parathyroid hormone (PTH), acting via the same receptor, which is expressed in many tissues but most abundantly in kidney, bone, and growth plate cartilage. It apparently has significant actions during development, but it is uncertain whether PTHrP circulates at all or has any function in normal human beings. The structure of the gene for human PTHrP is more complex than that of PTH, and varying molecular forms exist, including proteins of 141, 139, and 173 amino acids, which share a significant homology with parathyroid hormone.

**phenylthiocarbamoyl p.**, PTC p., the p. formed by combination of phenylisothiocyanate and an  $\alpha$ -amino group of a peptide. *SEE ALSO* phenylthiohydantoin.

**S p.**, *SEE* S protein.

**sigma p.**, a p. with one end bonded to a point within the chain, usually by means of the disulfide group of a cystine residue, so that only one end of the p. is free; so called since the p. chain has then the rough shape of the Greek letter sigma; e.g., oxytocin.

**p. synthetase** [EC 6.3.2.x], any enzyme that catalyzes the synthesis of peptide bonds, with the concomitant hydrolysis of a nucleoside triphosphate.

**vasoactive intestinal p.**, *syn* vasoactive intestinal polypeptide.

**pep-ti-der-gic** (pep-ti-der'jik). Referring to nerve cells or fibers that are believed to employ small peptide molecules as their neurotransmitter. [peptide + *G. ergon*, work]

**pep-ti-do-gly-can** (pep'ti-dō-glī'kan). A compound containing amino acids (or peptides) linked to sugars, with the latter preponderant. Cf. glycopeptide. *syn* mucopeptide (2).

**pep-ti-doid** (pep'ti-doyd). A condensation product of two amino acids involving at least one condensing group other than the  $\alpha$ -carboxyl or  $\alpha$ -amino group; e.g., glutathione.

**pep-ti-do-lyt-ic** (pep'ti-dō-lit'ik). Causing the cleavage or digestion of peptides. [peptide + *G. lytikos*, solvent]

**pep-ti-dyl di-pep-ti-dase A** (pep'ti-dil). A zinc-containing hydrolase cleaving C-terminal dipeptides from a variety of substrates, including angiotensin I, which is converted to angiotensin II and histidylleucine (an important step in the metabolism of certain vasopressor agents). Drugs that inhibit it are used to treat hypertension and congestive heart failure. *syn* angiotensin-converting enzyme, carboxycathepsin, dipeptidyl carboxypeptidase, kinase II, peptidase P.

**pep-tid-yl-trans-fer-ase** (pep-tī'dil-trans'fer-ās). The enzyme responsible for the formation of the peptide bond on the ribosome during protein biosynthesis, peptidyl-tRNA<sup>1</sup> + aminoacyl-tRNA<sup>2</sup>  $\rightarrow$  tRNA<sup>1</sup> + peptidylaminoacyl-tRNA<sup>2</sup>.

**pep-ti-za-tion** (pep-ti-zā'shūn). In colloid chemistry, an increase in the degree of dispersion, tending toward a uniform distribution of the dispersed phase.

**Pep-to-coc-ca-ce-ae** (pep'tō-kok-ā'sē-ē). A family of nonmotile, nonsporeforming, anaerobic bacteria (order Eubacteriales) containing Gram-positive (staining may be equivocal) cocci, 0.5–1.6  $\mu$ m in diameter, which occur singly, in pairs, chains, tetrads, and irregular masses but not in three-dimensional, cubic packets. These organisms are chemoorganotrophic and have complex nutritional requirements. Carbohydrates may or may not be fermented by these organisms, which produce gas, principally CO<sub>2</sub> and usually H<sub>2</sub>, from amino acids, or carbohydrates, or both. They are found in the mouth and intestinal and respiratory tracts of humans and other animals; they are frequently found in normal and pathologic human female urogenital tracts.

**Pep-to-coc-cus** (pep'tō-kok'ūs). A genus of nonmotile, anaerobic, chemoorganotrophic bacteria (family Peptococcaceae) containing Gram-positive, spherical cells that occur singly, in pairs, tetrads, or irregular masses, and rarely in short chains. They are frequently found in association with pathologic conditions. The type species is *P. niger*. [*G. peptō*, to digest, + *kokkos*, berry]

*P. aero'genes*, former name for *Peptostreptococcus asaccharolyticus*.

*P. constellatus*, a bacterial species found in tonsils, purulent pleurisy, appendix, the nose, throat, and gums, and infrequently on the skin and in the vagina.

*P. niger*, a bacterial species found once, in the urine of an aged woman; type species of the genus *P.*

**pep-to-crin-ine** (pep-tō-krin'ēn). An extract of the intestinal mucosa resembling secretin.

**pep-to-gen-ic**, **pep-tog-e-nous** (pep-tō-jen'ik, pep-toj'ē-nūs). 1. Producing peptones. 2. Promoting digestion.

**pep-toid** (pep'tōyd). A peptide with one or more non-amino acyl groups (e.g., sugar, lipid, etc.) covalently linked to the peptide.

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